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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/033,055 | 12/27/2001 | Ronald M. Burch | 200.1079CON | 7860 |

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DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

| EXAMINER | |
|---|---|
| CELSA, BENNETT M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1639 | |

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/033,055 | BURCH ET AL. | |
| | Examiner | Art Unit | |
| | Bennett Celsa | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *38-44 and 46-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-44,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/27/01&11/29/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### Status of the Claims

Claims 38-44 and 46-47 are currently pending and under consideration..

### *Election/Restriction*

1. Applicant's election without traverse of Group II (claims 38-44 and 46-47: methods using celecoxib and oxycodone) in the correspondence dated 6/14/04 is acknowledged.

### *Priority*

Applicant should update the cross-reference to parent application which has subsequently issued as a patent.

### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 38-44 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. US Pat. No. 4,569,937 (2/86) and Penning et al. J. Med. Chem. Vol. 40(9) (April 1997) pages 1347-1365.

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of :

a. a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof; and

b. ibuprofen (a non-steroidal anti-inflammatory drug or NSAID: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof,

in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present claim 47:See col. 2)

with oxycodone amounts of about 5 mgs-600mgs (compare to present claim 46).

The Baker reference teaches oral administration (e.g. see present claim 39), which can be coadministered in a "single dosage form" (e.g. see col. 3-8: and present claim 40) or sequentially administered (e.g. as in present claim 42; see i.e. col. 8-9 ; ".. mice are dosed sequentially..."). The Baker et al. reference teach that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is "unexpectedly enhanced" or synergistic "i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components", thereby permitting "reduced dosages of narcotic analgesics" (e.g. oxycodone) AND

which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components" resulting from high dosages of oxycodone or NSAID's such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32 (e.g. compare to present 43 and 44 "reduced" active ingredients). Accordingly, Baker would teach the use of therapeutic and subtherapeutic amounts of oxycodone and/or ibuprofen in view of the synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular patient., including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

The Baker analgesic composition differs from that presently claimed in that it fails to teach the substitution of celecoxib for ibuprofen, or alternatively, the further incorporation of (e.g. encompassed by "consisting essentially of") celecoxib into the Baker compositions.

Penning et al. teach both *in vitro* and *in vivo* (up to phase 2 clinical trials) that the selective COX2 inhibitor celecoxib (SC-58635):

a. had potent anti-inflammatory activity equivalent to NSAID's without the gastric toxicity side-effect of the NSAID's (e.g. celecoxib had no acute GI toxicity in rats at doses of up to 200 mg/kg and no chronic GI toxicity at doses up to 600 mg/kg);

b. has good bioavailability, is well distributed, and has an excellent safety profile;

c. is at least as potent against pain as aspirin in a phase 1 human clinical dental pain study.

See Penning abstract; page 1347; pages 1352-1354; Tables1-10.

Accordingly, one of ordinary skill in the art would have been motivated to substitute celecoxib for ibuprofen in the Baker reference compositions in light of the Penning reference teaching that celecoxib is analgesically potent with less side effects (e.g. as compared to NSAIDS e.g ibuprofen) in both *in vitro* and *in vivo* models, including humans.

Alternatively, one of ordinary skill in the art would have been motivated to incorporate celecoxib, with its potent analgesia and reduced side-effects, into the Baker ibuprofen/oxycodone compositions in order to reduce the amounts (e.g. therapeutic/subtherapeutic) of ibuprofen/oxycodone in order to avoid the side effects (e.g addiction) and/or toxicity resulting from ibuprofen/oxycodone. Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting celecoxib (for ibuprofen) or supplementing Baker's composition with celecoxib in light of the benefits of celecoxib (potent analgesia/decreased side effect as compared to NSAID's e.g. ibuprofen) as taught by the Penning reference.

4. Claims 38-44 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over as the Baker et al. '937 and Penning et al. references applied to claims 38-44 and 46-47 above, and further in view of Mayer et al. US Pat. No. 5,834,479 (11/98).

The teaching of the Baker and Penning et al. Reference as recited above is hereby incorporated by reference in its entirety.

To the extent that the Baker and Penning et al. references fail to teach the administration of the analgesia active agent (e.g. celecoxib) "before, ... with, or after" administration of the oxycodone" (particularly before/after ) (e.g. see present claim 42) the Mayer et al. Reference is cited.

The Mayer et al. reference teaches that analgesia effectiveness of an analgesia active agent (e.g. a NSAID, such as ibuprofen see i.e. table in col. 7) can be "significantly enhanced" by administering (e.g. oral administration) the active agent "prior to, with or following the administration of an analgesia enhancer" (e.g. a nontoxic NMDA receptor blocker and/or a nontoxic substance that blocks at least one major intracellular consequence of NMDA receptor activation) such as "dextromethorphan", which is the D-isomer of codeine . See e.g. col. 1; patent claims.

Accordingly, the Mayer et al. reference provides motivation to one of ordinary skill in the art to not only co- administer different analgesic agents to achieve enhanced analgesia, but to also administer the NSAID prior or subsequent to the second analgesic agent i.e. an analgesia enhancer, which includes codeine or its derivatives (e.g. dextromethorphan, dextrorphan, oxycodone etc.) .

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker and Penning reference teaching by administering one of the analgesic active agents (e.g. celecoxib) "before, ... with, or after" administration of the second analgesic agent (e.g. oxycodone) in order to obtain significantly enhanced analgesia.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
June 29, 2004